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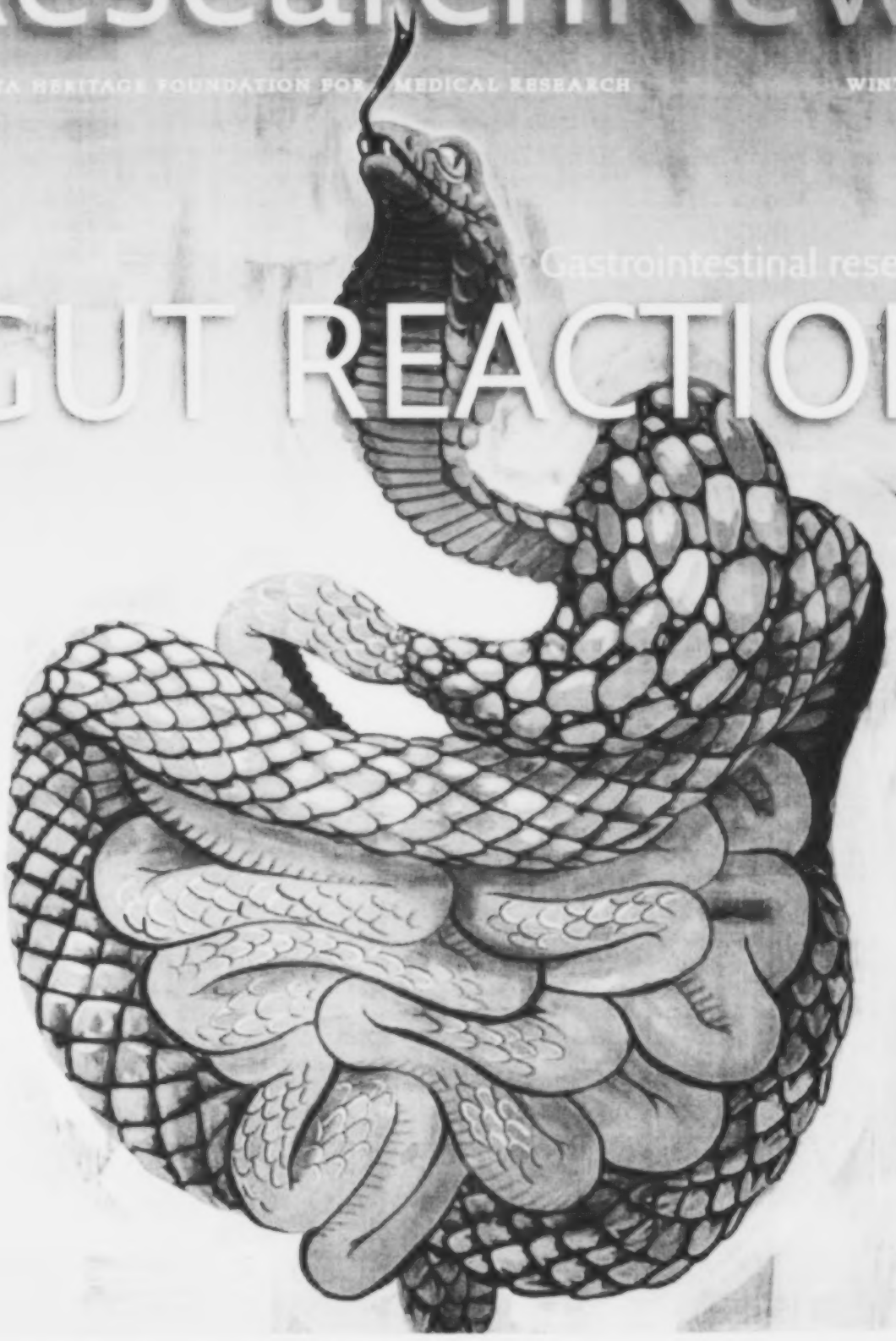
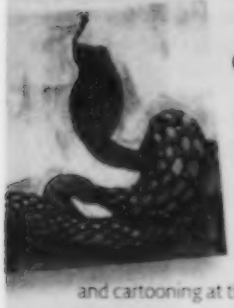
ResearchNews

ALBERTA HERITAGE FOUNDATION FOR MEDICAL RESEARCH WINTER 2009



Gastrointestinal research

GUT REACTION



On the cover

Genevieve Simms completed a Bachelor of Design in Illustration at the Alberta College of Art and Design in Calgary and studied illustration and cartooning at the School of Visual Arts in New York. She now works as an illustrator in Edmonton. Her clients have included *Canadian Business, The Globe and Mail, Avenue Calgary, and Avenue Edmonton*. You can see more of her work at **www.genevievesimms.com**

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WINTER 2009

FEATURES

AHFMR MISSION

AHFMR supports a community of researchers who generate knowledge, the application of which improves the health and quality of life of Albertans and people throughout the world. AHFMR's long-term commitment is to fund health research based on international standards of excellence and carried out by new and established investigators and researchers in training.

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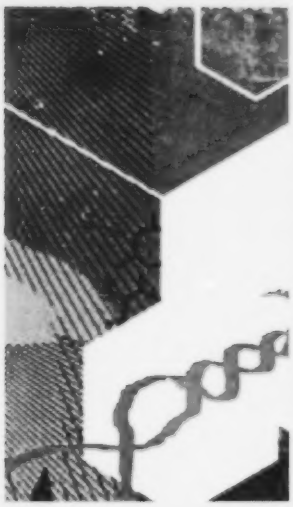

IN EVERY ISSUE

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Understanding the modern scientist

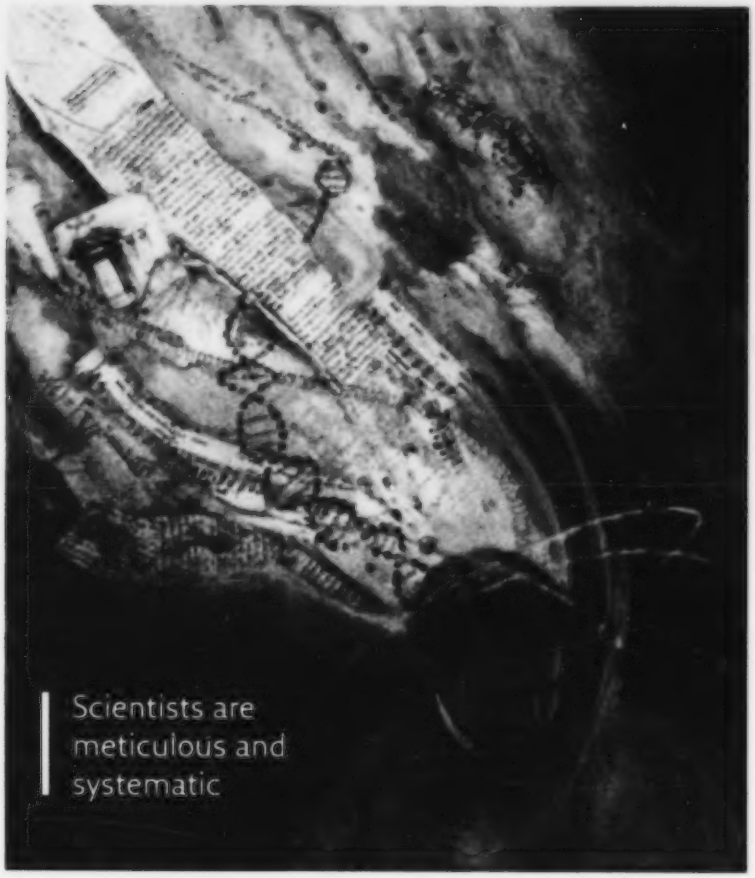
Almost every day we hear about new research studies offering the hope of treatments for conditions such as cancer and arthritis. Who are the scientists behind these studies? Does it matter?

STORY BY JANET HARVEY / ILLUSTRATION BY VEER

EVERY ISSUE OF THIS MAGAZINE introduces readers to a number of researchers in the health and biomedical field, and provides a glimpse of the work they do. But who are these scientists? What makes them tick? And how do today's scientists differ from the scientists of the past? Harvard historian of science Dr. Steven Shapin offers some answers in his latest book, *The Scientific Life*.

"In past centuries, there was more of a conception of scientists as natural philosophers," he explains. "They were seen as pursuing a calling—the study of God's creations—and thus were viewed as morally superior and sometimes as divinely-inspired geniuses."

That notion was in decline by the end of the 19th century, according to Dr. Shapin. A number of factors were at work. As society's understanding of nature became more removed from the influence of religion and spirituality, the idea of scientists as people who performed morally uplifting work also tended to disappear. The notion of scientist as genius declined with the rise of the *scientific method*, a mechanical means for producing and evaluating scientific knowledge. Scientists are now viewed as meticulous and systematic, rather than inspired and mor-

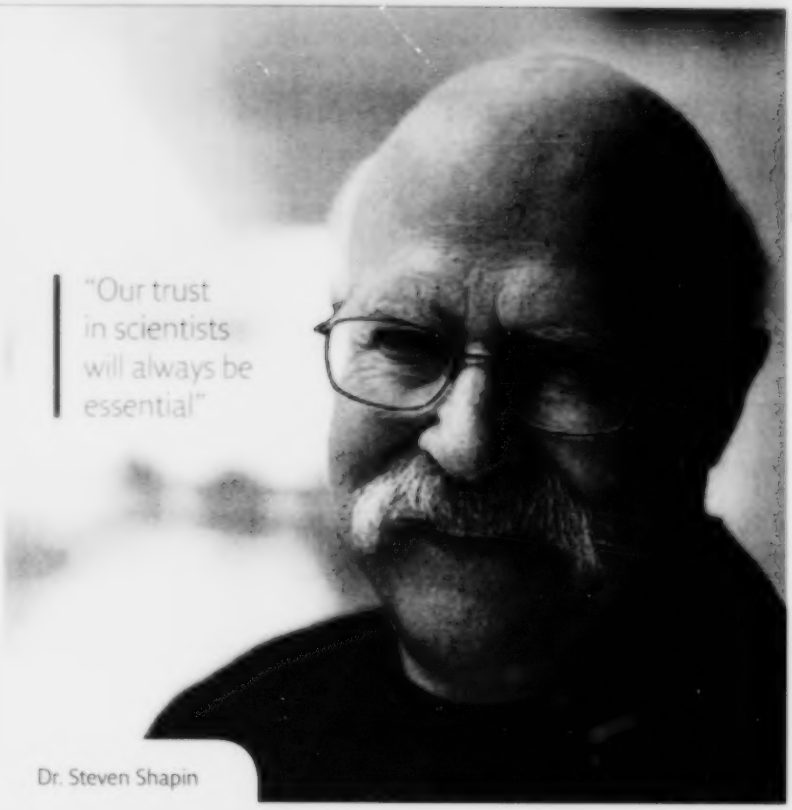


Scientists are meticulous and systematic

ally superior. In modern times, science has evolved into a job that comes with a paycheque, as opposed to a "calling" financed by people out of their own pockets, or supported by monarchs and other patrons.

What has taken the place of this historic view of the scientist, however, is less clear. In today's society, no one particular type of person becomes a scientist. In fact, the only trait common to scientists may be an intense fascination with determining how things work.

In spite of the shift away from the view of scientists as noble, some part of this perception remains. Witness the outrage whenever scientific fraud is discovered—when, for example, a South Korean researcher's claim to have successfully cloned human embryos was found to be false. "The very fact of this moral outrage is a sign that we expect scientists to tell the truth," explains Dr. Shapin. "Integrity is still supposed to come with the territory." In fact, all research relies on the integrity of individual scientists, because only a small proportion of experiments will ever be replicated. Scientists can't learn how things work if they falsify, fudge, or distort. "This is why the question of who is the modern scientist is important," says Dr. Shapin. "When we want to know whether information is reliable, we often seek to know who speaks for that knowledge—is it a trusted spokesperson? Our trust in scientists and in the institutions they represent will always be essential."



"Our trust in scientists will always be essential"

Dr. Steven Shapin

Dr. Shapin's knowledge of modern science comes partly from his own experience. After completing a degree in biology followed by some post-graduate genetics, he switched gears entirely to pursue studies in the history of science. What made him decide he wasn't a scientist himself? "I was training to be a scientist but found I was much more interested in thinking about science than in doing it. In science, you have to love the process of going into the lab and doing experiments—but what I loved was the scientific ideas, and trying to understand the flow of science in history and the relations between science and other forms of culture. I was always more of a humanist and I found the history of science a very satisfying field." *

About the researcher

Dr. Steven Shapin is Franklin L. Ford professor in the Department of the History of Science at Harvard University in Cambridge, Massachusetts.

Dr. Shapin will speak at the ***AHFMR Making Connections*** conference, which takes place from May 10 to 12, 2009 in Jasper, Alberta. More information is available at www.ahfmr.ab.ca/connects/conference or by e-mailing connects@ahfmr.ab.ca

Vertigo

Can a simple exercise cure it?

STORY BY CONNIE BRYSON / ILLUSTRATION BY BYRON EGGENSCHWILER / PHOTO BY TRUDIE LEE

About this column

AHFMR frequently receives letters requesting information about Heritage research or about various medical conditions. "Responding to the reader" is a *Research News* feature intended to provide up-to-date information related to readers' questions, with the help of experts in the Alberta research community. AHFMR cannot provide medical advice, however; please consult your family physician about your specific health concerns.

THE EXERCISE IN QUESTION is called the Epley manoeuvre—after Dr. John Epley, who developed the procedure in 1992. And yes, it can be very effective at treating a particular kind of vertigo called *benign paroxysmal positional vertigo* (BPPV). We asked Dr. Jacob Jaremko more about BPPV. He is an Edmonton radiologist who also works for a company that manufactures a device to help BPPV sufferers perform the Epley manoeuvre on their own.

First, it's important to understand the differences between dizziness and vertigo. When people say they are dizzy, they usually mean they feel light-headed. *Dizziness* can be a precursor to fainting; it may be brought on by a number of things, including low blood pressure or simply standing up too quickly. *Vertigo*, on the other hand, is the sensation of spinning; and it is less common than dizziness.

> Crystals called canaliths get into the semicircular canals

If you have true vertigo, the single most likely diagnosis will be BPPV. It accounts for at least 20% of all vertigo. The older you are, the more likely it is that your vertigo will be of this type. Symptoms are almost always precipitated by a change of position of the head—getting out of bed, rolling over in bed, tipping the head back, or bending forward. Attacks are often sudden and severe, and may be experienced when lying down or standing up. Typically they last no more than 30 seconds and occur in spells. In addition to the spinning sensation, many patients complain of light-headedness, nausea, imbalance, and, in severe cases, sensitivity to head movements in all directions.

> The trouble stems from the inner ear

The trouble stems from the inner ear; specifically, from a tiny organ called the *vestibular labyrinth*. The labyrinth is made up of semicircular canals that contain fluid and fine, hair-like sensors that monitor the rotation of your head. In BPPV, crystals called *canaliths*, which are normally present in another part of the ear, get into the semicircular canals. They cause the nerves in the ear to send false signals to the brain about position. The result is a spinning sensation. The Epley manoeuvre is designed to tilt the head in a series of positions that move the canaliths out of the semicircular canals. This manoeuvre is the standard of practice in the offices of many *otolaryngologists* (specialists who treat ear, nose, and throat disorders). Its success rate has been reported at 80% to 90% with a single manoeuvre. For patients who do not respond to this treatment, surgery is a safe and highly effective alternative.

Vertigo is the sensation of spinning

BPPV is common, but it's not the only type of vertigo. Consider the following statements:

- My vertigo lasts only seconds or minutes, never hours or days.
- I can bring on the symptoms by assuming certain head positions.
- It feels as though either the room or my body is spinning.
- My problem is not associated with a change in my hearing or a noise in my ears.

If these statements apply to you, it is very likely that you have BPPV, caused by the migration of canalith crystals. However, because there are many other possible causes of vertigo (including cardiovascular disease, stroke, and viral infection), the best course of action is to see your doctor for a diagnosis. ❋

About the researcher
Edmonton radiologist **Dr. Jacob Jaremko** is the advancement officer for Clearwater Clinical Ltd., the Calgary-based company that produces the DizzyFIX device mentioned in the *Cool Tools* article. In 2002 he won the Dr. Lionel E. McLeod Health Research Scholarship, awarded annually by AHFMR to an outstanding student at the University of Alberta, the University of Calgary, or the University of British Columbia for research related to human health.

Cool tools

The DizzyFIX

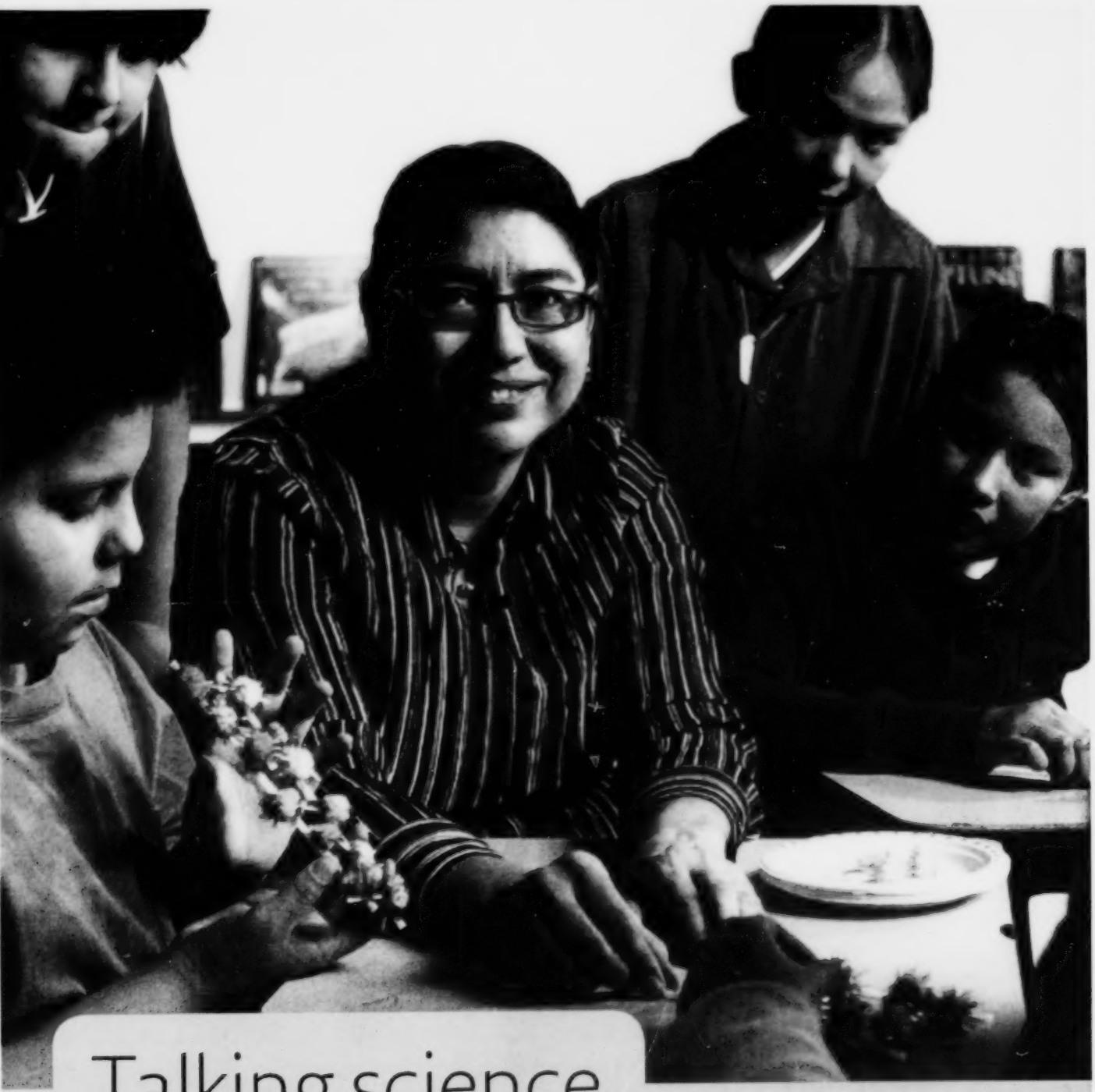
The idea for the DizzyFIX came to Dr. Matthew Bromwich while he was doing his residency in otolaryngology at the University of Western Ontario. There he studied with Dr. Lorne Parnes, one of the world's leading authorities on the type of vertigo known as BPPV. The experience got him thinking about a way to help patients do the repositioning manoeuvre that treats BPPV. As many as 50% of people with BPPV will experience at least one relapse, and many will have repeated relapses. Rather than wait for appointments with specialists, he thought, they could treat recurrent episodes quickly and effectively themselves—with the right sort of help.

Enter the DizzyFIX. The device is attached to a baseball cap, and the patient guides a little green ball through an oil-filled tube by means of a sequence of head movements. When the ball has been moved through the tube successfully, the repositioning manoeuvre is complete. Clinical trials have shown that the device is as effective as treatment in a doctor's office: in nearly 90% of patients, symptoms simply go away.

In 2005 Dr. Bromwich teamed up with friends and family to set up Calgary-based Clearwater Clinical Ltd. The company was formed to market the DizzyFIX and to serve as an incubator for other inventions. The DizzyFIX has been on sale in Canada since 2007. It received FDA approval in the United States in September 2008. AHFMR provided technology commercialization funding to help pay marketing evaluation and patenting costs.

Dr. Jacob Jaremko joined the Clearwater team as advancement officer in 2005. "Our focus now is getting DizzyFIX known among physicians and physiotherapists—basically, any medical professional who treats people with vertigo. This is a device that really works."

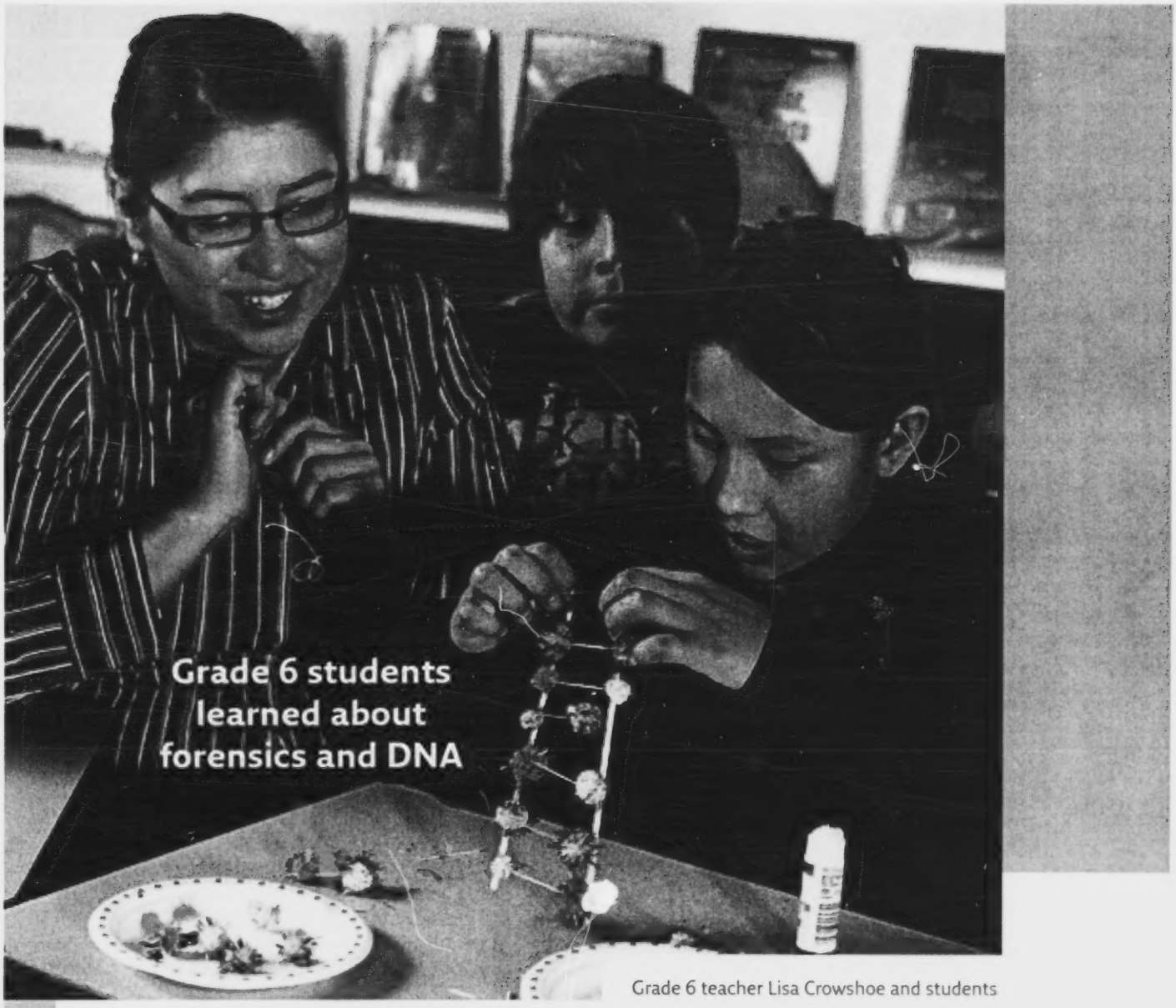
For more information on the DizzyFIX go to **www.dizzyfix.com** ❋



Talking science on the Blood Reserve

STORY BY JANET HARVEY
PHOTOS BY TRUDIE LEE

AHFMR offers free science workshops to teachers and students through its Education and Community Outreach program. This past fall the program took the show on the road—to the Blood Reserve in southern Alberta.



Grade 6 teacher Lisa Crowshoe and students

When they hear the word scientist, most kids of elementary and junior-high age probably envision someone in a white lab coat with crazy hair. But anyone who has ever wondered why something is a certain way, or how something works, has the makings of a scientist.

"Science is everywhere around us: we're living it," says Dr. Zenobia Ali. Dr. Ali, a former AHFMR Student now works with the Let's Talk Science (LTS) Partnership Program at the University of Calgary, along with Dr. Wendy Hutchins. Drs. Ali and Hutchins have also been contracted to run AHFMR's outreach programs in southern Alberta. "If you have ever questioned or observed something in the world around you, you are engaging in science, whether you realize it or not." This is an important message, one that AHFMR's Education and Community Outreach (ECO) Program wants students and teachers to hear. And AHFMR is starting to take the message on the road, reaching out to reserve schools that do not have the resources to teach hands-on science themselves.

Let's Talk Science is a nationwide initiative that aims to promote science among youth. In partnership with the Calgary branch, AHFMR offers science workshops for students of almost any age on

topics related to the human body. The workshops are normally held in state-of-the-art facilities at the University of Calgary's Faculty of Medicine. But they can also be brought to the classroom and tailored to the needs of the specific class. Tatsikiisaapo'p Middle School principal Mike Bruised Head chose this option when he approached the program staff about bringing hands-on science to the teachers and students of the Blood Reserve in Standoff, Alberta.

To introduce the workshops, ECO presenters held a workshop for teachers at the Standoff school. It began with some role-playing: The staff attended a "dinner", hosted by the presenters, at which almost everyone became ill. The challenge was to determine which food was the culprit, and why. During the same session, presenters described the various workshops LTS offers for students, and explained how they can be tailored to different grades.

On a separate day Dr. Ali and graduate student presenters returned to the Blood Reserve to deliver two student workshops on topics that fit with the provincial curriculum. Grade 6 students learned about forensics and DNA; Grade 8 students studied the cell. Since the school has no laboratory, the presenters brought along microscopes, pipettes, gloves, and other materials that would be required.

> AHFMR offers science workshops for students of almost any age

In the Grade 6 workshop, students learned to isolate DNA samples—using common substances found in kitchens, so they could go home and show their families what they had learned. The students also made candy models of the DNA double helix out of licorice and jujubes. "The kids were in awe," says Dr. Ali. "The Grade 6 students were excited just to wear the gloves, but they were also pretty happy to eat the candy."

Grade 6 teacher Lisa Crowshoe agrees. "The presentation on DNA was an excellent starting point for my students for when they begin this unit. They got to see the intricacy of DNA samples and I got to witness my students being very involved with the hands-on activities using the equipment provided by the presenters. They loved being scientists!"

In the Grade 8 workshop, volunteers taught the kids the differences between plant and animal cells. Students learned to stain blood films: They worked with prepared slides containing drops of blood, and introduced dyes to highlight certain features. Then they examined different types of blood cells under microscopes.

Since reserve schools often see students drop out by Grade 7, the hope is that engaging kids in science will motivate some of them to continue. The ECO program staff is also looking for ways to provide mentorship to students who show an interest, in order to encourage them to continue in science.

"Since this outstanding experience, I have recommended the workshops to other teachers," adds Lisa Crowshoe. "It got my students excited about science, and I hope others will be just as enthused about the program." ❋

About the researcher

Dr. Zenobia Ali is an assistant with AHFMR's ECO Program. She is also an adjunct assistant professor in the Department of Biochemistry and Molecular Biology at the University of Calgary, where she is an education coordinator for the Biotechnology Training Centre.

Recommended websites

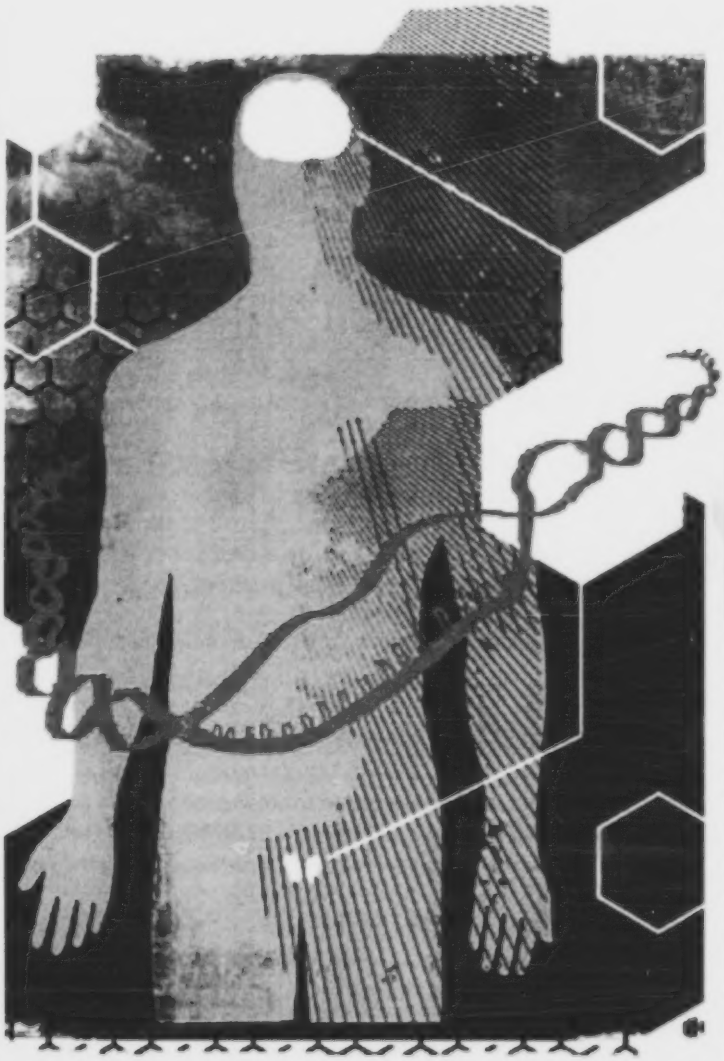
AHFMR Education and Community Outreach workshops for teachers and students
http://www.ahfmr.ab.ca/communication.php

Let's Talk Science
http://webapps2.ucalgary.ca/~lts

Safeguarding memory and more

Dr. Ki-Young Lee's pioneering research has shed new light on an enzyme originally thought to exist only in the brain

STORY BY SHEELAGH MATTHEWS / ILLUSTRATION BY WARREN HEISE



"Without memory, there is no happiness," claims AHFMR Senior Scholar Dr. Ki-Young Lee. It is memory that harnesses the brain's ability to make new connections when we are learning. But it is also memory that allows us to relive the happy days of our youth, our first loves, our children's early lives, and our achievements at work. Neurodegenerative diseases such as Alzheimer's rob us of our memories.

Dr. Lee, originally from Korea, found himself Alberta-bound in 1993, attracted by an AHFMR award and the prospect of being able to concentrate on his major research interest. Feeling amply rewarded by his work—and his proximity to the Rockies—he decided to settle in Calgary.

For more than a decade Dr. Lee has specialized in researching an enzyme called *cyclin-dependent kinase 5* (Cdk5), which regulates the division, differentiation, and death of cells. He is regarded as a pioneer and leader in this field. He has been studying abnormal activity of this enzyme in Alzheimer's disease. Recently, however, he has expanded his investigations to include its role in other devastating health problems, such as brain cancer, kidney disease, infertility, and birth defects.

Dr. Lee found that too much or too little Cdk5 activity could lead to disease. For example, in 1999

Dr. Lee is regarded as a pioneer and leader in this field

Dr. Ki-Young Lee

he and his team discovered that elevated activity of the enzyme is a feature of brains affected by Alzheimer's disease. Their recent studies suggest that Cdk5 is also involved in the spread of brain tumours.

The breakthrough came when Dr. Lee and his team discovered that Cdk5 activity exists outside of the brain. Although the enzyme is most abundant in the brain, a significant level is also found in the *testes*—the male reproductive organs that produce sperm and testosterone. Dr. Lee points out that there are several similarities between sperm cells in the testes and nerve cells in the brain. Both are non-dividing; both regulate their secretions; both migrate during development; and the growth of the *flagella* (sperm "tails") resembles the growth of the *axons* that project from nerve cells.

Following up on this, Dr. Lee has begun investigations into the development of sperm flagella. The sperm flagellum is a specialized form of *primary cillium*—a microscopic hairlike extension of the cell membrane. The functions of primary cilia are believed to range from sensing and orientation to signalling and navigation. Dr. Lee has gathered evidence that Cdk5 plays an important role in regulating the development of primary cilia, and he expects the enzyme is probably also an important player in disorders related to that development.

Since primary cilia are found on nearly all cells of the human body, it's hardly surprising that faulty cilia are involved in a wide range of diseases and conditions. For example, a certain developmental defect can produce sperm flagella that are incapable of movement, one cause of infertility. Another type of ciliary defect can result in the complete left-right reversal of internal organs in a fetus. Other research implicates defective cilia in such diverse conditions as polycystic kidney disease, retinal degeneration, certain types of obesity, diabetes, neural tube defects, lung disease, and mental disorders.

Dr. Lee hopes that his Cdk5 research will lead him to understand the basic science that underlies these disorders, thereby helping to pave the way for the development of treatments. ✲

About the researcher

Dr. Ki-Young Lee is an *AHFMR Senior Scholar* and an associate professor in the Department of Cell Biology and Anatomy at the University of Calgary.

Selected publications

Rosales JL, Lee K-Y. Extraneuronal roles of cyclin-dependent kinase 5. *BioEssays*. 2006 Oct; 28(10):1023-1034.

Recommended website

Southern Alberta Cancer Research Institute
http://www.sacri.ucalgary.ca

GUT REACTI

STORY BY CONNIE BRYSON / ILLUSTRATIONS BY GENEVIEVE SIMMS AND VEER

GUT REACTI

Hundreds of thousands of Canadians suffer from such gastrointestinal problems as inflammatory bowel disease. And Alberta's rates are among the highest in the country.

STORY BY CONNIE BRYSON / ILLUSTRATIONS BY GENEVIEVE SIMMS AND VEER

ON

"You know that children can get this disease? I have two kids—I can't imagine a child going through this. I barely made it myself."

PHOTO BY ANDY DEVLIN/EDMONTON OILERS HOCKEY CLUB

THESE ARE THE WORDS OF EDMONTON OILER FERNANDO PISANI. HIS BATTLE WITH *ULCERATIVE COLITIS* (INFLAMMATION OF THE LARGE INTESTINE) BEGAN IN 2005.

Although he managed to continue playing hockey, a serious flare-up in 2007 took him out of the lineup for 26 games. Suffering from almost constant diarrhea, dramatic weight loss, fatigue, and depression, Pisani thought his hockey career was over—along with his life as he knew it. But a new drug that blocks the inflammation process started him on the road to recovery. Today he is on medication, back on the ice with the Oilers, and feeling fine.

Pisani's struggles are all too familiar to many of us. More than 200,000 Canadians are seriously affected by *inflammatory bowel disease* (IBD). This is an umbrella term for a group of diseases that involve inflammation of the intestines. The two main diseases in the group are ulcerative colitis and Crohn's disease.

"Canada has one of the highest incidences of IBD in the world; and, within Canada, Alberta has some of the highest rates," says Dr. Richard Fedorak, a gastroenterologist and IBD researcher at the University of Alberta. "There is a concerted effort to find out what causes IBD and why the rates are so high in this province."

More than 30 genetic defects are associated with IBD, but faulty genes on their own are not enough to trigger illness. It is widely believed that exposure to something in the environment—such as a bacterium or a virus—sets off the

Inflammatory bowel disease (IBD) involves inflammation of the intestines

runaway inflammation that is the hallmark of this group of diseases.

Dr. Fedorak notes that for the past 20 years there has been an intensive research effort focused on IBD in Calgary and Edmonton. "The exciting message is that we have been working on the basic science of IBD for years. The research has now come to the *translational* stage—we are taking what we know and applying that to patients."

About the researcher

Dr. Richard Fedorak is a full professor and the director of the Division of Gastroenterology, in the Department of Medicine at the University of Alberta. He leads the Centre of Excellence for Gastrointestinal Inflammation and Immunity Research (CEGIIR). He is a former recipient of AHFMR funding.

Selected publication

Huynh HQ, deBruyn J, Guan L, Diaz H, Li M, Girgis S, Turner J, Fedorak R, Madsen K. Probiotic preparation VSL#3 induces remission in children with mild to moderate acute ulcerative colitis: a pilot study. *Inflammatory Bowel Diseases*. DOI:10.1002/ibd.20816. Epub 2008 Dec 9. Available from: http://www3.interscience.wiley.com/journal/121555067/abstract

TURNING OFF INFLAMMATION, REBOOTING THE IMMUNE SYSTEM

■ One of the Alberta scientists working on translational research is AHFMR Scholar Dr. Paul Beck at the University of Calgary. He is a *clinician-scientist*. In other words, he is a physician—in his case a gastroenterologist—who also heads up a formal research program. "Clinician-scientists have a unique view on disease, how it comes on, and its interactions with drugs. We are on the front lines when it comes to seeing patients, and we know enough basic science to say, 'It might be this.' Our observations can be particularly relevant."

"I believe that looking at cell death may give us clues to IBD," says Dr. Beck. "If we could figure out the switch, we could design a drug to target it." The hypothesis is that in IBD there is no switch to turn off the inflammation. Instead, T cells (white blood cells whose specialty is to kill off any infection by means of inflammation) continue to respond and make the inflammation steadily worse. In the course of his investigation Dr. Beck has found two molecules that are

responsible for stopping the inflammatory response by killing T cells.

Looking ahead, Dr. Beck is particularly excited by the potential of stem-cell transplants in the treatment of IBD. Worldwide to date, about 100 people with Crohn's disease have been treated with stem-cell transplants. Crohn's sufferers are genetically predisposed to the disease, which is first triggered when they come into contact with a particular environmental stimulus. The immune system responds, resulting in symptoms that blight the lives of sufferers. Transplantation "reboots" the immune system, restoring it to the state it was in before the onset of the disease.

The procedure involves three steps: (1) harvesting *stem cells* from the patient's own bone marrow (these are the body's "master cells", which can be directed to grow into cells of any other type); (2) killing off the patient's remaining stem cells, to knock out the entire immune system; and (3) re-introducing the previously harvested stem cells into the patient's bone marrow, where they give rise to a new generation of immune cells that function normally. Because all steps involve the patient's own cells, there is virtually no risk of rejection.

"The flaw in this treatment is that you are giving patients back their same immune system with the defective genes," says Dr. Beck, "so they are still susceptible to developing Crohn's. The extension would be to do gene therapy on the stem cells themselves to correct the defects before you give the stem cells back to the patients. We don't have the technology to do this right now, but I think it's not far off."

EAT YOUR BACTERIA

■ IT'S NOT SURPRISING that we humans are sometimes referred to as "superorganisms" made up of bacteria and human cells—we have trillions of bacteria living in our gut, and they outnumber, by far, our own cells. This notion might be a little...creepy, but the reality is that we need those bugs in our gut.

"The human race evolved with bacteria, and we've developed a symbiotic relationship with bacteria," says AHFMR Senior Scholar Dr. Karen Madsen from the University of Alberta. "Our intestines provide a home for bacteria, and the bacteria are vital to our health because they aid in proper digestion and [they] support immune-system functioning. Signals pass back and forth between the bacteria in our gut, the epithelial cells that line the intestine, and the cells of the immune system."

Probiotics are good bacteria that can benefit their host

About the researcher

AHFMR Scholar **Dr. Paul Beck** is an associate professor in the Division of Gastroenterology, part of the Faculty of Medicine at the University of Calgary. He is a member of the Gastrointestinal Research Group there.

Selected publication

Beck PL, Li Y, Wong J, Chen C-W, Keenan CM, Sharkey KA, McCafferty D-M. Inducible nitric oxide synthase from bone marrow-derived cells plays a critical role in regulating colonic inflammation. *Gastroenterology*. 2007 May;132(5):1778–1790.

Dr. Madsen studies how intestinal bacteria influence the development and progression of IBD. One of the characteristics of IBD is a "leaky gut". This occurs when spaces develop between the cells of the intestinal wall, and toxins—in the form of displaced bacteria and fragments of food—are allowed to leak into the bloodstream. Some bacteria that live in the gut release small *peptides* (fragments of proteins) that make the intestine less leaky. "We're investigating how these peptides work and how they signal the epithelial cells," explains Dr. Madsen. "We want to isolate them, in the hope that we could develop a treatment for those patients who have 'leaky guts'."

Another characteristic of IBD is an imbalance in the bacteria that live in the intestine. The strains of intestinal bacteria in most IBD patients are different from those in healthy people. A key question is whether the changes in bacterial populations are a consequence of inflammation or a cause of it. We might expect active inflammation to give rise to some obvious changes, but research by Dr. Madsen and others has shown that many changes occur *before* inflammation.

These observations have led to the use of *probiotics*—so-called good bacteria—to treat IBD. Several clinical trials have shown that probiotics are effective in treating ulcerative colitis. In recent studies, both adult and pediatric patients with ulcerative colitis were given probiotic supplements, with the result that their remission rates increased significantly. However, for reasons unknown, probiotics do not appear to be as effective in treating Crohn's disease.

Probiotics are effective in treating ulcerative colitis

Dr. Madsen points out that treatment with probiotics does not mean simply adding bacteria to certain foods. "In some diseases, we may not want to treat people with live bacteria. It would be much better to isolate the active agents. That's why basic research on identifying these agents and how they work is so important."

Quick Facts

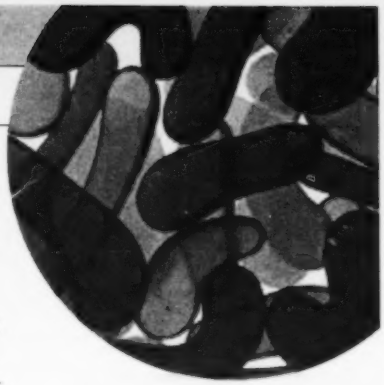
Probiotics are living microorganisms, usually bacteria, that can affect the host in a beneficial manner.

Prebiotics are indigestible food ingredients that stimulate the growth and activity of probiotic bacteria already established in the intestine.

Synbiotics are combinations of a probiotic and a prebiotic.

About the researcher
AHFMR Senior Scholar **Dr. Karen Madsen** is a full professor in the Division of Gastroenterology, part of the Department of Medicine at the University of Alberta.

Selected publication
Ewaschuk JB, Diaz H, M[illegible]ings L, Diederichs B, Dmytrash A, Backer J, Looijer-van Langen M, Madsen KL. Secreted bioactive factors from Bifidobacterium infantis enhance epithelial cell barrier function. *American Journal of Physiology – Gastrointestinal and Liver Physiology*. 2008;295: G1025-G1034.



EAT YOUR WORMS

■ IT'S HARD TO IMAGINE that infection with a parasitic worm could be good for you, but there's evidence to show that such a treatment may be useful in IBD. Microscopic worm eggs, mixed into a drink and swallowed by the patient, hatch in the intestine and grow into small organisms. Then the immune system reacts to these organisms, eventually getting rid of them. Researchers believe that the interaction between the worms and the immune system triggers regulatory pathways to stop the rampant inflammation that is the hallmark of IBD.

But how does treatment with worms *really* work? This question captivates AHFMR Scientist Dr. Derek McKay: It is the focus of one of the major research programs in his lab at the University of Calgary. His group works with parasitic *helminths*, a scientific classification for various types of parasitic worms that live in the intestines of humans and animals.

"We want to understand how treatment with a parasite can block inflammation," explains Dr. McKay. "The idea is to identify all the cells, mediators, and pathways that are involved. Pilot studies to date have shown that having people ingest helminth eggs is feasible. But there's always a risk in introducing any species where it is not meant to be. If we understand how the worms actually interact with the immune system, we may be able to identify molecules that could be used as drugs to treat IBD."

Experiments on animal models in Dr. McKay's lab show that the immune system of the host responds to the worms by producing an anti-inflammatory molecule. But clinical trials using this molecule in humans have been unsuccessful. Dr. McKay's results in animals suggest that success may depend on eliciting this anti-inflammatory response naturally, in the right place and at the right time.

Asked to speculate about how this might translate to people, Dr. McKay gives this scenario: It might be possible to give IBD patients a helminth infection to trigger the interleukin-10 response on purpose. The patients would then be treated with drugs to clear the worm infection. But their immune systems would "remember" the infection. Subsequently, if the IBD flared up, the patients could be treated with a worm antigen rather than the live worm. The *antigen*—a substance that, by definition, prompts the immune response—would trigger the appropriate reaction and treat the inflammation.

"This is very exciting, but it is some ways down the road," notes Dr. McKay. "That's the beauty of model systems; they can give you clues to what's happening in humans."

"We want to understand how treatment with a parasite can block inflammation"

About the researcher
AHFMR Scientist
Dr. Derek McKay
is a full professor in the Department of Physiology and Biophysics at the University of Calgary.

Selected publication

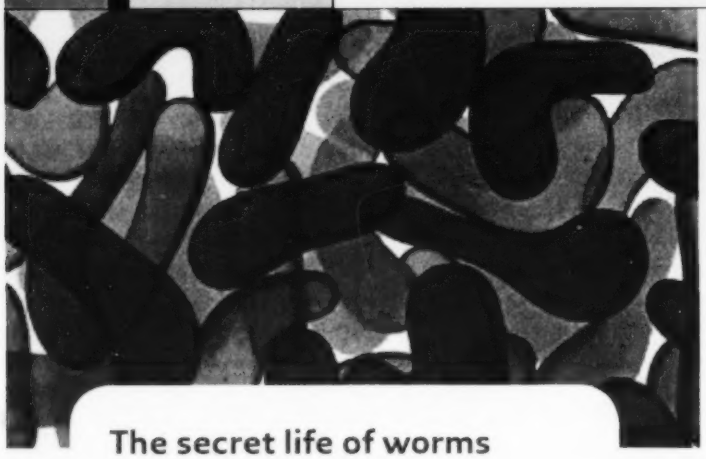
Hunter MM, Wang A, Hirota CL, McKay DM. Neutralizing anti-IL-10 antibody blocks the protective effect of tapeworm infection in a murine model of chemically induced colitis. *Journal of Immunology*. 2005 June 1;174(11):7368-7375

Recommended websites

Crohn's and Colitis Foundation of Canada
http://www.ccfc.ca

Canadian Association of Gastroenterology
http://www.cag-acg.org/

Canadian Digestive Health Foundation
http://www.cdhf.ca/



The secret life of worms

Don't bother to look for AHFMR Scientist Dr. James McGhee in his office most Monday mornings—he'll be at the worm meeting.

Each week, 20 or 30 researchers from five University of Calgary labs get together to discuss their research on *Caenorhabditis elegans*, a tiny roundworm about one millimetre in length that lives in the soil. Dr. McGhee and his colleagues are not alone; thousands of researchers around the world study this worm. The popularity of *C. elegans* lies in the fact that, although it is a multicellular organism with about 1,000 cells, it is simple enough to be studied in great detail. Scientists have mapped out the developmental fate of every cell in *C. elegans*; in other words, they know where the cell comes from and what every cell will turn into.

> Worms are masters of digestion

"I set out to understand how an organism makes an intestine: what genes are turned on in the various parts of the digestive tract, what genes control them, and how it's all coordinated," says Dr. McGhee. "The beauty of studying this in *C. elegans* is that it is delightfully simple compared to our intestines. The entire intestine derives from one cell in the eight-celled embryo."

The worms are also masters of digestion. A single *C. elegans* eats double or triple its body mass—several million bacteria—every day. Each bacterium spends less than two minutes in the intestine; but in that time the worm can extract all the nutrients it needs.

Dr. McGhee's team has assembled a comprehensive list of all the genes produced in the *C. elegans* intestine, both in the embryo and in the adult. Their work points to one "master regulator", a specialized type of protein called a *transcription factor* that controls the process by which the information in a gene is made into something functional. This particular protein is produced in every cell of the intestine, from the time when the intestine consists of only two cells right through to the end of the worm's life. One of Dr. McGhee's goals is a complete analysis of the many roles played by this transcription factor in driving the development of the intestine.

"Of course, worms don't have the complex gastrointestinal system of mammals, but at a fundamental level the genes we are looking at in *C. elegans* are the same genes that control our own intestines," notes Dr. McGhee. "The power of this tiny worm as an experimental system is that understanding these fundamental processes may help explain how the regulatory pathways in the human intestine can go wrong and cause individuals to be susceptible to gastrointestinal diseases." ❋

About the researcher
AHFMR Scientist **Dr. James McGhee** holds a Tier 1 Canada Research Chair in Developmental Biology. He is a full professor in the Department of Biochemistry and Molecular Biology and the Department of Medical Genetics in the Faculty of Medicine at the University of Calgary. Dr. McGhee is a member of the Genes and Development Research Group as well as the Institute of Maternal and Child Health.

Selected publication

McGhee JD, Sleumer MC, Bilenky M, Wong K, McKay SJ, Goszczynski B, Tian H, Krich ND, Khattra J, Holt RA, Baillie DL, Kohara Y, Marra MA, Jones SJM, Moerman DG, Robertson AG. The ELT-2 GATA-factor and the global regulation of transcription in the C. elegans intestine. *Developmental Biology*. 2007 Feb 15;302(2):627-645.

Recommended website

Wormbook: The Online Review of C. elegans Biology.
See "The C. elegans intestine" in the section: Developmental control.
http://www.wormbook.org/chapters/www_intestine/intestine.html

THE NERVOUS GUT

■ WHEN WE TALK ABOUT THE NERVOUS SYSTEM, we usually think of the brain, the spinal cord, and associated nerves. But there's actually another complex set of nerves in our body. The gastrointestinal system has its own set: the *enteric nervous system*. There are as many nerve cells in the enteric nervous system as there are in the spinal cord. This rich nervous environment is the subject of AHFMR Scientist Dr. Keith Sharkey's research. He holds the Crohn's and Colitis Chair in IBD Research at the University of Calgary.

"One of most interesting aspects of the enteric nervous system is the constant two-way communication between the gut and the brain, and the brain and the gut. It's not just the brain affecting the gut; the gut also affects the brain. Sorting this out is fascinating work."

Dr. Sharkey's interest in the enteric nervous system has taken his research in a number of directions, one of which is the study of a particular class of chemical messengers called *endocannabinoids*. These molecules, which are produced in the body, act on the same receptors as *cannabinoids* (the active ingredient in marijuana). Dr. Sharkey's lab has made some discoveries that illuminate the role of endocannabinoids in controlling nausea and vomiting. In 2005 his team found a new cannabinoid receptor in the brain. Unlike the first receptor, which was discovered in 1990, this one reduces nausea and vomiting without mind-altering effects.

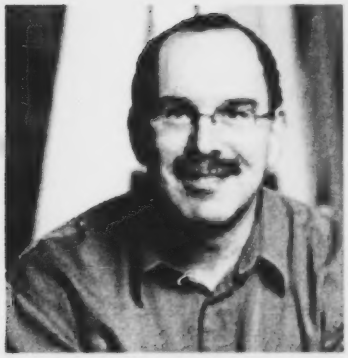
"Simply knowing about these receptors is just scratching the surface," notes Dr. Sharkey. "Now we are working on understanding how they are regulated. If we could get a handle on this, we would be in a position to target these receptors and use endocannabinoids therapeutically for treating inflammation, suppressing appetite, and increasing metabolism. There's a lot of potential."

In addition to his research on the gastrointestinal system, Dr. Sharkey studies the neurobiology of obesity. He examines

"It's not just the brain affecting the gut; the gut also affects the brain."

the communication between the brain and the enteric nervous system and how that communication controls food intake. Specifically, he is looking at stimuli produced by the gut that make us want to eat or to stop eating. These stimuli may be the key to preventing overeating.

"Understanding the digestive system is a much bigger challenge than many people realize," says Dr. Sharkey. "The digestive system has a number of jobs to do: digest food in the right place and at the right time; protect us from the digestive process itself, which is inherently able to digest *us*; and protect us from toxic or hazardous elements in our food. And it is all so elegantly regulated." ❋



About the researcher
AHFMR Scientist **Dr. Keith Sharkey** is Crohn's and Colitis Chair in IBD Research and a full professor in the Department of Physiology and Biophysics and the Department of Medicine at the University of Calgary. He is also a member of the Hotchkiss Brain Institute and the Snyder Institute of Infection, Immunity, and Inflammation.

Selected publication

Storr MA, Keenan CM, Emmerdinger D, Zhang H, Yüce B, Sibaev A, Massa F, Buckley NE, Lutz B, Göke B, Brand S, Patel KD, Sharkey KA. Targeting endocannabinoid degradation protects against experimental colitis in mice: involvement of CB_1 and CB_2 receptors. *Journal of Molecular Medicine*. 2008 Aug;86(8):925-936.

Recommended websites

Enteric Nervous System
http://www.scholarpedia.org/article/Enteric_nervous_system

Dr. Sharkey's website
http://www.ucalgary.ca/~ksharkey/home.shtml

New partnership boosts IBD research

AHFMR and the Crohn's and Colitis Foundation of Canada (CCFC) have signed a partnership agreement aimed at stepping up research on inflammatory bowel disease (IBD). The agreement will enable more doctoral students and post-doctoral fellows to be supported financially while they carry out research on IBD. The CCFC and AHFMR will offer four training awards over the next two years. The awards are intended primarily for Alberta students who want to study at the doctoral level or do post-doctoral training, elsewhere in Canada or abroad. For more information go to **www.ahfmr.ab.ca/grants/gastrointestinal.php**

CHALLENGING THE IDEA OF AUTOIMMUNITY

Dr. Andrew Mason's research has been a flashpoint for controversy. This University of Alberta researcher and AHFMR Senior Scholar is a *hepatologist*, a physician who treats patients with liver disease. He has been challenging the widely held belief that many gastrointestinal diseases are caused by the body turning against its own cells. He suspects that at least some of these diseases are really viral diseases, and his evidence comes from his own research. He has identified a virus associated with *primary biliary cirrhosis* (PBC), a disease in which the bile ducts of the liver are slowly destroyed, and scarring of liver tissue results. Although medication can slow the progression of the disease, a substantial proportion of patients will eventually require liver transplants. PBC is the reason behind more than 10% of all liver transplants worldwide. It is considered an autoimmune disease.

> Dr. Mason has found a virus associated with a liver disease called PBC

"I've always been skeptical about how autoimmunity is hypothesized as the cause for so many diseases," says Dr. Mason. "If you take a look at livers from patients with PBC or autoimmune hepatitis and compare them to livers from patients with hepatitis B or C, they don't look that much different. We know that hepatitis B and C are viruses—so why not look for viruses?"

That's exactly what he has done. Dr. Mason has found a virus, called *human betaretrovirus*, associated with PBC. He has isolated the virus in patients, grown it in the lab, and has also shown that it causes a similar disease in animals. To prove that the virus actually infects patients with PBC, he has identified "integration sites" where the virus puts a copy of itself into the human genome. However, clinical trials using antiviral therapy to treat PBC have not been conclusive. While patients have shown significant improvement in biochemistry and symptoms, there was not enough improvement to demonstrate a substantial change in the disease.

Undeterred, Dr. Mason is attempting to organize another clinical trial, this time using *highly active antiretroviral therapy* (HAART), the powerful therapy behind the drop in the AIDS-related death rate in developed countries. He is also conducting "virus discovery" studies on a number of other diseases. His team has already identified a virus associated with *primary sclerosing cholangitis*, another disease that damages bile ducts.

Not everyone buys into the hypothesis. "People are always skeptical when someone claims that they have discovered a virus that causes 'autoimmune' disease but it also took a long time for the scientific community to accept that ulcers were caused by bacteria. Long-term, I hope I see antiviral therapy as a routine treatment for PBC. I believe it's our best chance of eradicating this disease as a progressive disease that usually leads to a liver transplant." ✻

About the researcher
AHFMR Senior Scholar
Dr. Andrew Mason is an associate professor in the Division of Gastroenterology, part of the Faculty of Medicine and Dentistry at the University of Alberta.

Selected publication

Xu L, Shen Z, Guo L, Fodera B, Keogh A, Joplin R, O'Donnell B, Aitken J, Carman W, Neuberger J, Mason A. Does a betaretrovirus infection trigger primary biliary cirrhosis? *Proceedings of the National Academy of Sciences of the United States of America*. 2003 Jul 8;100(14):8454-8459.

Recommended websites

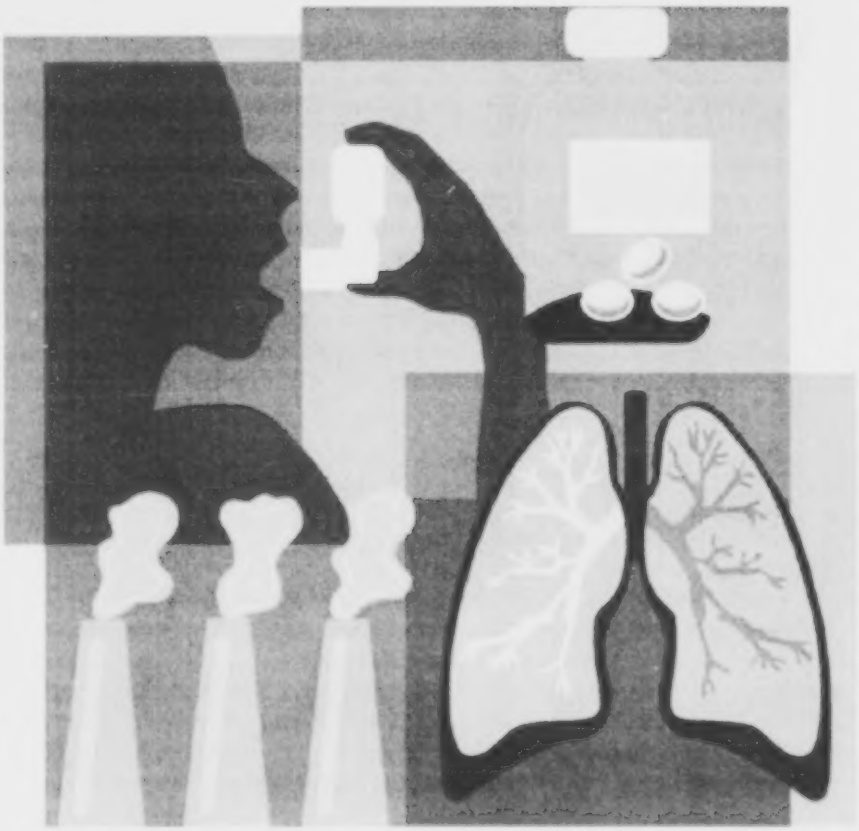
Canadian Liver Foundation
http://www.liver.ca

Canadian PBC Society
http://www.pbc-society.ca

Fighting for breath

Dr. Lisa Cameron hopes to solve some of the genetic mysteries behind asthma and allergies.

STORY BY TARA NARWANI / ILLUSTRATION BY VEER



MOST OF US TAKE OUR BREATHING FOR GRANTED. We expect each breath to be easy. But people with asthma face a disease that threatens their ability to breathe. Inhaling the wrong substance can trigger an asthma attack. If they have allergies as well, they may make the asthma symptoms worse.

■ **WHAT HAPPENS IN AN ALLERGIC ASTHMA ATTACK?** When the body's immune system detects a foreign substance (the allergen) and sounds the alarm, the muscles surrounding the airways tighten and go into spasm. The result: shortness of breath, coughing, and a characteristic wheezing sound as the person struggles to breathe. To fight the inhaled invader cells, immune cells in the airways release histamine and other inflammatory chemicals, which start to inflame the airway walls. This is the first phase of the attack; it may or may not be followed by a second phase several hours later.

The second phase generally lasts longer than the first, and symptoms can be even stronger. In addition to airway muscle constriction, the airway tissue becomes inflamed and swollen, making the air passages even narrower. The lining of the airways releases extra mucus—which takes up even more of the precious air space—in an attempt to envelop the invaders and carry them out of the body. The most severe attacks can lead to suffocation.

Some cases of allergic asthma can be managed by avoiding the allergen—the specific substance that induces the condition. Most, however, require medication. Because each individual reacts differently to asthma, and current asthma medications

vary in their effectiveness on particular symptoms, there is always the need for new treatments. "Asthma is characterized by a range of symptoms that arise as a consequence of both the genetic and environmental circumstances of each patient," explains AHFMR Scholar Dr. Lisa Cameron. In the future, she believes, treatments will be tailored to the unique circumstances of each patient.

Dr. Cameron investigates the role of allergies in the development of asthma. She wants to determine what controls a particular gene that plays a role in the allergic response in people who have asthma. The immune response in people with allergies is, by definition, abnormal; that is, they react quite severely when they inhale certain substances that would elicit very little or no response at all in the average person. But if they also have asthma, their allergic reaction will exacerbate their asthma symptoms.

> Allergic reactions exacerbate asthma symptoms

The early phase of an asthma attack is associated with acute, immediate asthma symptoms. It may or may not be followed by a second phase. This later phase contributes to the chronic symptoms of asthma. "The late-phase response creates a perpetual cycle that continues to release chemicals that restrict breathing," she explains. It is this phase that is of particular interest to Dr. Cameron; her work focuses on a specific component of this cycle and how it is regulated.

A type of immune cell called a Th2 lymphocyte plays a key role in the late-phase allergic response. Each Th2 cell has a receptor protein called CRTh2 on its surface. Allergy conditions alert this protein to produce certain chemical messengers. The messengers, in turn, recruit more immune cells, which increases the inflammatory response. This can become a runaway process. The resulting inflammation of the airways in asthmatic lungs becomes chronic and can cause permanent changes to lung tissue.

Because CRTh2 is involved in the late-phase allergic response, Dr. Cameron is investigating the factors controlling the activation of the gene that produces this protein. She and her colleagues have discovered that changes in the genetic sequence for CRTh2 can influence the development of allergies in people with asthma. Now she is conducting tests to see how these changes cause increased activation of the gene, which in turn can increase the inflammatory response.

> "The future of asthma treatment is undoubtedly personalized medicine"

The fundamental question is whether changes in CRTh2 gene activation can change the allergic response, and ultimately reduce the severity of an individual's asthma symptoms, or even lessen that individual's propensity to develop the disease in the first place. If so, this knowledge could lead to a range of new asthma medications targeted at individuals with specific genetic variations.

Dr. Cameron's passion for her work is clear when she talks about its possible impact. "Given the complexity of the disease, the future of asthma treatment is undoubtedly personalized medicine. This frontier can only be opened up, however, with continued progress in basic research. This dual goal—to understand the biology of human disease and to improve asthma treatment and the life of these patients—is what makes the work exciting." ❋

About the researcher
AHFMR Scholar
Dr. Lisa Cameron is an assistant professor in the Department of Medicine at the University of Alberta, where she is a member of the Pulmonary Research Group.

Recommended website
The Lung Association (Canada)
http://www.lung.ca

Selected Publications

Quapp R, Madsen N, Cameron L. Characterization of the promoter of human CRTh2, a prostaglandin D2 receptor. *Biochemical and Biophysical Research Communications*. 2007;363:948.

Summer stories

Last summer, Lesley Baldwin and Joshua Bezanson took a break from hectic university schedules to become reporters at CBC Radio.

STORY BY LAURA LY / PHOTOS BY DUSTIN DELFS AND TRUDIE LEE

Joshua Bezanson

Lesley Baldwin

WE LIVE IN A WORLD OF INSTANT INFORMATION. But despite this 24/7 availability, messages important to people's health and well-being sometimes lack impact. This past summer, thanks to AHFMR's Media Fellowship Program, two students got the opportunity to draw upon their own scientific backgrounds to bring stories about science and medical research to the airwaves of Alberta.

■ JOSHUA BEZANSON, a University of Calgary student who is preparing for medical school, and Lesley Baldwin, a Ph.D. student in medical physics at the University of Alberta, were the recipients of the 2008 AHFMR Media Fellowships. Bezanson was posted at CBC Radio in Calgary, and Baldwin at CBC Radio in Edmonton.

AHFMR's Media Fellowship Program, which started in 1991, provides university students a unique opportunity to spend a summer working at media outlets in Alberta. The 12-week posting is intended to enhance the coverage of issues related to science and technology, while enabling young scientists to find out how events and ideas become news.

Baldwin and Bezanson applied to the program because they saw room for improvement in the quality and effectiveness of media stories about science and medical research. "A lot of science impacts us; and it's always in the public's best interest to have some idea of what's going on in the world of science," says Baldwin.

But science can get bogged down with technical terminology and statistics, and these aspects make research less comprehensible to the public. Bezanson notes, "The media play an important role in reporting research. The challenge that comes with that—and the responsibility—is to remain accurate and yet bring it to a level that ordinary people can understand and appreciate."

Both students met this challenge by producing radio series

Science reporting is like storytelling

related to their own interests. Bezanson's weekly series, titled *Prairie Care*, profiled Alberta healthcare workers such as physicians, hospice workers, nurse practitioners, naturopathic doctors, and technicians in the field of nuclear medicine. *Prairie Care* was intended to put a human face on the healthcare system. "The real stories were hidden in the fascinating day-to-day work of people providing healthcare or conducting research," explains Bezanson. The last three installments aired nationally and received positive feedback.

Baldwin's *Cancer Research in Alberta* series profiled scientists involved in cutting-edge cancer research. The topic is close to her heart, as she herself conducts research at the Cross Cancer Institute with the support of an AHFMR Studentship. She looks for ways to correct geometric imperfections in magnetic resonance images so that these images can be used to plan more effective radiation treatments. *Magnetic resonance imaging* (MRI) uses magnets, radio waves, and a computer to produce detailed images of structures such as organs, soft tissue, and bone.

Baldwin also created a series called *Inquiring Minds* to celebrate the University of Alberta's centennial in 2008. She featured historical landmarks in research with U of A connections: the development of sonar technology, for example, and the role of Dr. James Collip in developing insulin for clinical use in 1921.

At the outset Baldwin was a researcher with little media experience; whereas Bezanson was a journalism graduate who had limited knowledge of medical research. Despite their different backgrounds, they emerged with a common understanding about the challenges involved in reporting science stories to the public.

Bezanson compares the skill of science-reporting to the art of storytelling: how well you tell the story determines the impact of that story on the audience. The two agree that the most valuable thing they learned last summer was how to tell a good story—a skill that will prove useful for Baldwin's career as a researcher and Bezanson's future as a physician.

The students also gained a balanced perspective about media and science. Bezanson developed a critical eye for research and an understanding of the research process. Baldwin gained an appreciation for science from an outsider's perspective: "It's nice to poke your head above water and just take a look at the huge diversity of really great work going on. It helps you see your own work from a new angle." ✻

Visit www.ahfmr.ab.ca/communications/fellowship.php for more information on the AHFMR Media Fellowship Program.

AHFMR funding partners

The Alberta Heritage Foundation for Medical Research (AHFMR) has committed more than $1 billion to Alberta's health-research community. The Foundation also relies on the contributions of many partners in building and sustaining health research in this province. In addition to AHFMR support, researchers featured in this issue of *Research News* also receive funding from:

- Alberta Cancer Board
- Alberta Health and Wellness
- Canada Research Chairs
- Canadian Association of Gastroenterology
- Canadian Association for the Study of Liver
- Canadian Institutes of Health Research
- Canadian Liver Foundation
- Canadian Lung Association
- Crohn's and Colitis Foundation of Canada
- Heart and Stroke Foundation of Canada
- Natural Sciences and Engineering Research Council of Canada
- SickKids Foundation

Following **up**

Engaging communities to prevent chronic disease

STORY BY TARA NARWANI / PHOTO BY DUSTIN DELFS

Dr. Kim Raine

■ THIRTY YEARS AGO the task of significantly reducing smoking rates in the Canadian population might have seemed an impossible one. Policy initiatives such as mandatory smoke-free spaces and increased taxes on tobacco, however, have achieved that very result. The key to success was recognizing that changes at a societal level could affect the health of the individual.

Using a similar approach, AHFMR Health Senior Scholar Dr. Kim Raine is tackling the problem of rising rates of chronic diseases. Raine is co-director of Healthy Alberta Communities, a three-year project that receives funding from Alberta Health and Wellness. The project develops community-based resources that can overcome barriers to healthy lifestyle decisions. Its goal is to reduce the incidence of chronic diseases, such as diabetes and cancer, through environmental changes—changes designed to promote increased levels of physical activity and better nutrition. The project researchers are working with four communities in the province: Edmonton-Norwood, Medicine Hat, St. Paul, and Bonnyville.

In 2005 Dr. Raine and her team began compiling data on the resources for health promotion available in each of these communities "For example, we wanted to know if there were safe places to walk, or places to buy healthy, affordable food," Raine explains. Working with community leaders, including mayors and businesspeople, Healthy Alberta Communities established a set of priorities to guide community development.

In Medicine Hat, for example, Healthy Alberta Communities worked with the local health region to extend the scope of community gardening. Now 60 new garden plots allow individuals and families to grow their own fresh fruit and vegetables. The project also helped the city to link up its trail systems, so as to promote more active forms of travel, such as cycling and walking.

As the anti-smoking campaigns demonstrate, it takes time for projects like this to show their impact on health. But Dr. Raine will not be discouraged. "I believe the only way that we can stem the tide of increasing chronic diseases is to change the environment: to make the healthy choice the easy choice." ✳

About the researcher
AHFMR Health Senior Scholar **Dr. Kim Raine** is a full professor at the Centre for Health Promotion Studies in the School of Public Health at the University of Alberta.

Recommended website
http://www.healthyalbertacommunities.com

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AHFMR 15th floor, 10104-103 Avenue Edmonton, AB T5J 4A7